Limits: **Publication Date to 1998/11/18**

- Search History will be lost after eight hours of inactivity.
- To combine searches use # before search number, e.g., #2 AND #6.
- Search numbers may not be continuous; all searches are represented.
- Click on query # to add to strategy

Search	Most Recent Queries	Time	Result
#10	Search **hypervariable region and insertion and binding affinity** Limits: **Publication Date to 1998/11/18**	10:04:05	3
#9	Search **hypervariable region and insertion** Limits: **Publication Date to 1998/11/18**	10:03:47	31
#8	Search **hypervariable region and humanize** Limits: **Publication Date to 1998/11/18**	10:03:13	0
#7	Search **hypervariable region and humanized** Limits: **Publication Date to 1998/11/18**	10:02:46	0
#6	Search **CDR H3 and humanized** Limits: **Publication Date to 1998/11/18**	09:59:39	0
#5	Search **CDR H3 and chimeric** Limits: **Publication Date to 1998/11/18**	09:59:08	3
#4	Search **CDR replacement** Limits: **Publication Date to 1998/11/18**	09:56:05	51
#3	Search **CDR replacement**	09:55:34	81
#2	Search **(CDR replacement) and ((increased or enhanced) and (biological activity))**	09:55:16	0
#1	Search **(CDR replacement) and ((increased or enhanced) and (binding affinity))**	09:54:14	2

Clear History

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Wednesday, April 12, 2006

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ	
☐	L10	L1 and ((increased or enhanced) same (biological adj activity))	100
☐	L9	L1 and ((increased or enhanced) same (binding adj affinity))	44
☐	L8	(muller yves)[IN]	4
☐	L7	(lowman henry b)[IN]	72
☐	L6	(chen yvonne m)[IN]	2
☐	L5	L4 and (CDR H3)	26
☐	L4	L3 and humanized	139
☐	L3	L2 and (biological adj activity)	144
☐	L2	L1 and (binding adj affinity)	206
☐	L1	((CDR adj replacement)and antibod?)	222

END OF SEARCH HISTORY

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Last logoff:  09apr06 14:16:58
Logon file001 12apr06 09:08:52
          *** ANNOUNCEMENTS ***
                    ***
NEW FILES RELEASED
***Regulatory Affairs Journals (File 183)
***Index Chemicus (File 302)
***Inspec (File 202)
                    ***
RELOADS COMPLETED
*** MEDLINE has been reloaded with the 2006 MeSH (Files 154 & 155)
*** The 2005 reload of the CLAIMS files (Files 340, 341, 942)
is now available online.

RESUMED UPDATING
***EDGARPLUS(TM)-Williams Act Filings (File 773)
***EDGARPLUS(TM)-Prospectuses (File 774)
***EDGARPLUS(TM)-Registration Statements (File 775)
***EDGARPLUS(TM)-6K,8K, and 10C Filings (File 776)
***EDGARPLUS(TM)-10-K & 20F Filings (File 778)
***EDGARPLUS(TM)-10-Q Filings (File 779)
***EDGARPLUS(TM)-Proxy Statements (File 780)
                    ***
Chemical Structure Searching now available in Prous Science Drug Data Report (F452),
IMS R&D Focus (F445/955), Pharmaprojects (F128/928), Beilstein
Facts (F390), Derwent Chemistry Resource (F355) and Index Chemicus
(File 302).
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 >>>a specific database by entering HELP NEWS <file number>.<<<
 * * *

File   1:ERIC 1966-2006/Mar (c) format only 2006 Dialog

      Set  Items  Description
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Cost is in DialUnits
?

FILE CAPLUS, BIOENG, BIOTECHNO, BIOTECHDS, ESBIOBASE
>>>"CAPLUS" is not a valid category or service name
>>>"BIOENG" is not a valid category or service name
>>>"BIOTECHNO" is not a valid category or service name
>>>"BIOTECHDS" is not a valid category or service name
>>>"ESBIOBASE" is not a valid category or service name
>>>No valid files specified
?

B 155, 159, 10, 203, 35, 5, 467, 73, 434, 34
       12apr06 09:10:13 User290558 Session D30.1
            $1.18    0.337 DialUnits File1
     $1.18  Estimated cost File1
     $0.53  INTERNET
     $1.71  Estimated cost this search
     $1.71  Estimated total session cost   0.337 DialUnits
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SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R) 1951-2006/Apr 12
         (c) format only 2006 Dialog
 *File 155: Medline has been reloaded. Some accession numbers
have changed.
  File 159:Cancerlit 1975-2002/Oct
         (c) format only 2002 Dialog
 *File 159: Cancerlit is no longer updating.
Please see HELP NEWS159.
  File  10:AGRICOLA 70-2006/Mar
         (c) format only 2006 Dialog
  File 203:AGRIS 1974-2006/Nov
         Dist by NAL, Intl Copr. All rights reserved
  File  35:Dissertation Abs Online 1861-2006/Mar
         (c) 2006 ProQuest Info&Learning
  File   5:Biosis Previews(R) 1969-2006/Apr W2
         (c) 2006 BIOSIS
  File 467:ExtraMED(tm) 2000/Dec
         (c) 2001 Informania Ltd.
 *File 467: F467 will close on February 1, 2006.                    7.
  File  73:EMBASE 1974-2006/Apr 11
         (c) 2006 Elsevier Science B.V.
  File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
         (c) 1998 Inst for Sci Info
  File  34:SciSearch(R) Cited Ref Sci 1990-2006/Apr W1
         (c) 2006 Inst for Sci Info

      Set  Items  Description
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?

S (CDR (3N) REPLACEMENT) AND ((INCREASE? OR ENHANCE?) SAME (BINDING AFFINITY))
>>>Invalid syntax
?

S (CDR (3N) REPLACEMENT) AND ((INCREASE? OR ENHANCE?) (S) (BINDING (N) AFFINITY))
Processing
Processed  10 of  10 files ...
Completed processing all files
           7350  CDR
         493341  REPLACEMENT
             58  CDR(3N)REPLACEMENT
        8540513  INCREASE?
        2308033  ENHANCE?
        3142874  BINDING
         863428  AFFINITY
          32729  (INCREASE? OR ENHANCE?)(S)BINDING(N)AFFINITY
      S1      0  (CDR (3N) REPLACEMENT) AND ((INCREASE? OR ENHANCE?) (S)
                 (BINDING (N) AFFINITY))
?

S (CDR (3N) REPLACEMENT) AND ((INCREASE? OR ENHANCE?) (S) (BIOLOGICAL (N) ACTIVITY))
Processing
Processed  10 of  10 files ...
Completed processing all files
           7350  CDR
         493341  REPLACEMENT
             58  CDR(3N)REPLACEMENT
        8540513  INCREASE?
        2308033  ENHANCE?
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         2055313  BIOLOGICAL
         6258060  ACTIVITY
           20567  (INCREASE? OR ENHANCE?)(S)BIOLOGICAL(N)ACTIVITY
      S2       0  (CDR (3N) REPLACEMENT) AND ((INCREASE? OR ENHANCE?) (S)
                  (BIOLOGICAL (N) ACTIVITY))
?

S (HYPERVARIABLE (N) REGION) AND (INSERTION) AND (BINDING (N) AFFINITY) OR (BIOLOGIC
Processing
           16361  HYPERVARIABLE
         3060479  REGION
            6808  HYPERVARIABLE(N)REGION
          295021  INSERTION
         3142874  BINDING
          863428  AFFINITY
          157558  BINDING(N)AFFINITY
         2055313  BIOLOGICAL
         6258060  ACTIVITY
          123545  BIOLOGICAL(N)ACTIVITY
      S3  123547  (HYPERVARIABLE (N) REGION) AND (INSERTION) AND (BINDING
                  (N) AFFINITY) OR (BIOLOGICAL (N) ACTIVITY)
?


Set     Items   Description
S1          0   (CDR (3N) REPLACEMENT) AND ((INCREASE? OR ENHANCE?) (S) (B-
             INDING (N) AFFINITY))
S2          0   (CDR (3N) REPLACEMENT) AND ((INCREASE? OR ENHANCE?) (S) (B-
             IOLOGICAL (N) ACTIVITY))
S3     123547   (HYPERVARIABLE (N) REGION) AND (INSERTION) AND (BINDING (N)
              AFFINITY) OR (BIOLOGICAL (N) ACTIVITY)
?

S (CDR (N) H3) AND CHIMERIC
            7350  CDR
           32904  H3
             281  CDR(N)H3
          102799  CHIMERIC
      S4      11  (CDR (N) H3) AND CHIMERIC
?

RD S4
      S5       3  RD S4  (unique items)
?

T S5/MEDIUM/1-3

  5/3/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2006 Dialog. All rts. reserv.

11475591   PMID: 9305727
 Sequence analysis and bacterial production of the anti-c-myc antibody
 9E10: the V(H) domain has an extended CDR-H3 and exhibits unusual
 solubility.
  Schiweck W; Buxbaum B; Schatzlein C; Neiss H G; Skerra A
  Institut fur Biochemie, Technische Hochschule, Darmstadt, Germany.
  FEBS letters (NETHERLANDS) Sep 1 1997, 414 (1) p33-8, ISSN
0014-5793--Print  Journal Code: 0155157
  Publishing Model Print
```

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

5/3/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10884313 PMID: 8683596
X-ray structure of the uncomplexed anti-tumor antibody BR96 and comparison with its antigen-bound form.
Sheriff S; Chang C Y; Jeffrey P D; Bajorath J
Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, USA.
Journal of molecular biology (ENGLAND) Jun 28 1996, 259 (5) p938-46, ISSN 0022-2836--Print Journal Code: 2985088R
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

5/3/3 (Item 1 from file: 35)
DIALOG(R)File 35:Dissertation Abs Online

02023821 ORDER NO: AADAA-I3134902
Construction and characterization of HRV14:HIV-1gp41 ELDKWA combinatorial libraries as sources of AIDS vaccine candidates
Author: Velasco, Paola Karla
Degree: Ph.D.
Year: 2004
Corporate Source/Institution: Rutgers The State University of New Jersey - New Brunswick (0190)
Source: VOLUME 65/06-B OF DISSERTATION ABSTRACTS INTERNATIONAL. PAGE 2927. 174 PAGES
?

Set	Items	Description
S1	0	(CDR (3N) REPLACEMENT) AND ((INCREASE? OR ENHANCE?) (S) (BINDING (N) AFFINITY))
S2	0	(CDR (3N) REPLACEMENT) AND ((INCREASE? OR ENHANCE?) (S) (BIOLOGICAL (N) ACTIVITY))
S3	123547	(HYPERVARIABLE (N) REGION) AND (INSERTION) AND (BINDING (N) AFFINITY) OR (BIOLOGICAL (N) ACTIVITY)
S4	11	(CDR (N) H3) AND CHIMERIC
S5	3	RD S4 (unique items)

?

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NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS	4	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS	5	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS	6	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS	7	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS	8	JAN 30	Saved answer limit increased
NEWS	9	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS	10	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS	11	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS	12	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS	13	FEB 28	MEDLINE/LMEDLINE reload improves functionality
NEWS	14	FEB 28	TOXCENTER reloaded with enhancements
NEWS	15	FEB 28	REGISTRY/ZREGISTRY enhanced with more experimental spectral property data
NEWS	16	MAR 01	INSPEC reloaded and enhanced
NEWS	17	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS	18	MAR 08	X.25 communication option no longer available after June 2006
NEWS	19	MAR 22	EMBASE is now updated on a daily basis
NEWS	20	APR 03	New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS	21	APR 03	Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
NEWS	22	APR 04	STN AnaVist $500 visualization usage credit offered

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
http://download.cas.org/express/v8.0-Discover/

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* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

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FILE 'HOME' ENTERED AT 10:21:13 ON 12 APR 2006

=> file caplus, bioeng, biotechno, biotechds, esbiobase
COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                              ENTRY    SESSION
FULL ESTIMATED COST                            0.21       0.21

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=> s (hypervariable (w) region) and chimer? and (CDR (w) H3)
L1            2 (HYPERVARIABLE (W) REGION) AND CHIMER? AND (CDR (W) H3)

=> duplicate remove l1
PROCESSING COMPLETED FOR L1
L2            2 DUPLICATE REMOVE L1 (0 DUPLICATES REMOVED)

=> d l2 bib abs 1-2

L2    ANSWER 1 OF 2  BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
AN    2005-13450  BIOTECHDS
TI    New binding molecule capable of binding to human NogoA polypeptide, human
      NiG, human NiG-D20, or human NogoA342-357, useful for treating nerve
      repair, Alzheimer's disease, Parkinson's disease, or amyotrophic lateral
      sclerosis;
         production of a monoclonal antibody, chimeric antibody or
         humanized antibody specific for NogoA and NiG useful for a disease
         immunotherapy application
AU    BARSKE C; FRENTZEL S; MIR A K; SCHWAB M E; VITALITI A
PA    NOVARTIS AG; NOVARTIS PHARMA GMBH; UNIV ZURICH
PI    WO 2005028508 31 Mar 2005
AI    WO 2004-EP10489 17 Sep 2004
PRAI  GB 2003-21997 19 Sep 2003; GB 2003-21997 19 Sep 2003
DT    Patent
LA    English
OS    WPI: 2005-242564 [25]
AN    2005-13450  BIOTECHDS
AB    DERWENT ABSTRACT:
      NOVELTY - A binding molecule comprises 221 or 238 amino acids (SEQ ID NO.
      2 or 3), and capable of binding to human NogoA polypeptide comprising
      1192 amino acids (SEQ ID NO. 5), human NiG comprising 819 amino acids
      (SEQ ID NO. 7), human NiG-D20 comprising 181 amino acids (SEQ ID NO. 24),
      or human NogoA342-357 comprising 18 amino acids (SEQ ID NO. 6) all given
      in the specification, with a dissociation constant of less than 1000 nM,
      is new.
           DETAILED DESCRIPTION - A binding molecule comprises 221 or 238 amino
      acids (SEQ ID NO. 2 or 3), and capable of binding to human NogoA
      polypeptide comprising 1192 amino acids (SEQ ID NO. 5), human NiG
      comprising 819 amino acids (SEQ ID NO. 7), human NiG-D20 comprising 181
      amino acids (SEQ ID NO. 24), or human NogoA342-357 comprising 18 amino
```

acids (SEQ ID NO. 6) all given in the specification, with a dissociation constant of less than 1000 nM, and comprises: (a) a first antigen binding site comprising in sequence the **hypervariable regions** CDR-H1, CDR-H2, and **CDR-H3**, where each of the **hypervariable regions** are at least 50 % homologous to their equivalent **hypervariable regions** CDR-H1-3A6 comprising a fully defined 10 amino acids (SEQ ID NO. 8), CDR-H2-3A6 comprising 17 amino acids (SEQ ID NO. 9), and **CDR-H3** -3A6 comprising 9 amino acids (SEQ ID NO. 10) all given in the specification; and (b) a second antigen binding site comprising in sequence the **hypervariable regions** CDR-L1, CDR-L2, and CDR-L3, where each of the **hypervariable regions** are at least 50 % homologous to their equivalent **hypervariable regions** CDR-L1-3A6 comprising 16 amino acids (SEQ ID NO. 11), CDR-L2-3A6 comprising 7 amino acids (SEQ ID NO. 12), and CDR-L3-3A6 comprising 9 amino acids (SEQ ID NO. 13) all given in the specification. INDEPENDENT CLAIMS are also included for the following: (1) a polynucleotide comprising: (a) polynucleotides encoding the binding molecule above; (b) polynucleotide sequences comprising fully defined 27-51 bp sequences (SEQ ID NO. 14-16) given in the specification; or (c) polynucleotide sequences comprising fully defined 21-48 bp sequences (SEQ ID NO. 17-19) given in the specification; (2) an expression vector comprising polynucleotides above, where the expression system or its part is capable of producing a polypeptide, when the expression system or its part is present in a compatible host cell; (3) an isolated host cell comprising the expression system above; (4) a pharmaceutical composition comprising the binding molecule in association with at least one pharmaceutical carrier or diluent; and (5) treating diseases associated with nerve repair.

BIOTECHNOLOGY - Preferred Binding Molecule: The binding molecule comprises at least one immunoglobulin heavy chain or its fragment which comprises a variable domain comprising in sequence the **hypervariable regions** CDR-H1-3A6 (SEQ ID NO. 8), CDR-H2-3A6 (SEQ ID NO. 9), and **CDR-H3**-3A6 (SEQ ID NO. 10) and the constant part or its fragment of a human heavy chain; and one immunoglobulin light chain or its fragment which comprises a variable domain comprising in sequence the **hypervariable regions** CDR-L1-3A6 (SEQ ID NO. 11), CDR-L2-3A6 (SEQ ID NO. 12), and CDR-L3-3A6 (SEQ ID NO. 13) and the constant part or its fragment of a human light chain; or its direct equivalents. The constant part or fragment of the human heavy chain is of the gamma4 type and the constant part or fragment of the human light chain is of the kappa type. Preferably, the binding molecule is a human or **chimeric** or humanized monoclonal antibody. Preferred Method: Treating diseases associated with nerve repair comprises administering to a subject in need of treatment an amount of the binding molecule above.

ACTIVITY - CNS-Gen; Neuroprotective; Nootropic; Antiparkinsonian; Antidiabetic; Ophthalmological. No biological data given.

MECHANISM OF ACTION - None given.

USE - The binding molecule is useful as a pharmaceutical, preferably in the treatment of nerve repair (claimed). It is also useful in the treatment of various diseases of the peripheral (PNS) and central (CNS) nervous system, e.g. neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, or amyotrophic lateral sclerosis. It can also be used for treating degenerative ocular disorders including diabetic retinopathy, age-related macular degeneration, or pathologic myopia.

ADMINISTRATION - Dosage is 1 microg/kg/day-1 mg/kg/day. It can be administered directly into the CNS intracranially or into the spine intrathecally to the lesioned site.

EXAMPLE - No relevant example given. (117 pages)

L2 ANSWER 2 OF 2 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
AN 2003-24971 BIOTECHDS

TI Making an antibody variant of a parent antibody specific to an antigen by identifying a target amino acid residue within the variable domain of the parent antibody and substituting the target residue with a different amino acid residue;
antibody production against antigen via plasmid expression in host cell for use in disease therapy and gene therapy

AU LOWMAN H B; MARVIN J S
PA GENENTECH INC

PI WO 2003068801 21 Aug 2003
AI WO 2003-US4184 11 Feb 2003
PRAI US 2002-409685 10 Sep 2002; US 2002-355895 11 Feb 2002
DT Patent
LA English
OS WPI: 2003-697521 [66]
AN 2003-24971 BIOTECHDS

AB DERWENT ABSTRACT:
NOVELTY - Making an Ab (Ab) variant of a parent Ab specific to an antigen comprising: (a) identifying a target amino acid residue within the variable domain of the parent Ab; and (b) substituting the target residue of step (1) with a different replacement amino acid residue such that the charge complementarity between the Ab and antigen is increased.

DETAILED DESCRIPTION - Making an Ab (Ab) variant of a parent Ab specific to an antigen by (a) identifying a target amino acid residue within the variable domain of the parent Ab, the target residue being an exposed residue in solution, in or adjacent to a **hypervariable region** or within about 20 Angstrom of the antigen when the parent Ab is bound to it; and (b) substituting the target residue of step (1) with a different replacement amino acid residue such that the charge complementarity between the Ab and antigen is increased. INDEPENDENT CLAIMS are also included for: (1) an Ab variant of a parent Ab which comprises an amino acid alteration in or adjacent to a **hypervariable region** of the parent Ab which increases charge complementarity between the Ab variant and an antigen to which it binds; (2) an isolated nucleic acid encoding the Ab variant; (3) a vector comprising the nucleic acid; (4) a host cell transformed with the nucleic acid; (5) a process of producing an Ab variant; and (6) a method for determining antigen association rate of an Ab.

BIOTECHNOLOGY - Preferred Method: Making an Ab variant of a parent Ab specific to an antigen further comprises: (a) producing the Ab variant in a host cell comprising nucleic acid encoding the Ab variant; and (b) conjugating the Ab variant produced by the host cell with a heterologous molecule. The target residue does not directly contact antigen when bound to it. It has at least about one third of its side chain surface area exposed to solvent. It is within at least about 16 Angstrom of the antigen when bound to it. The parent Ab is humanized, human or **chimeric** Ab. It is an Ab fragment, which is a Fab fragment. The Ab variant has a stronger binding affinity for the antigen than the parent Ab. The binding affinity of the Ab variant is at least about two fold stronger than the binding affinity of the parent Ab. The Ab variant has a faster association rate with the antigen than the parent Ab. The association rate of the Ab variant is at least about 5 or 10 fold faster than the association rate of the parent Ab. The Ab variant has 1-20 substitutions in the **hypervariable regions** compared to the parent Ab. Each of the substitutions increases charge complementarity between the Ab and antigen. The antigen is vascular endothelial growth factor (VEGF). The parent Ab comprises the heavy and light chain variable domains of a humanized anti-VEGF Ab consisting of Y0101, Y0317, F(ab)-12, Y0192, Y0238-3, Y0239-19, Y0313-2 or VNERK. The substitution is in a **hypervariable region** consisting of CDR L1, CDR L2, loop H1 or **CDR H3**. The substitution is at one or more of amino acid positions 26L, 27L, 28L, 30L, 31L, 32L, 50L, 52L, 53L, 54L, 56L, 93L or 94L of a light chain variable domain of the parent Ab, utilizing the residue numbering system according to Kabat. The substitution is at two or more of amino acid

positions 26L, 27L, 28L or 30L of a light chain variable domain of the parent Ab, at three or four of amino acid positions 26L, 27L, 28L or 30L of a light chain variable domain of the parent Ab or at one or more of amino acid positions 25H, 28H, 30H, 54H, 56H, 61H, 62H, 99H or 100aH of a heavy chain variable domain of the parent Ab. The antigen is tissue factor (TF). The parent Ab comprises the heavy and light chain variable domains of a humanized anti-TF Ab, which is D3H44. The antigen is HER2. The parent Ab comprises the heavy and light chain variable domains of a humanized anti-HER2 Ab, which is the rhuMAb 4D5. Preferred Ab: The Ab variant of a parent Ab which comprises an amino acid alteration in or adjacent to a **hypervariable region** of the parent Ab.
The alteration is an amino acid insertion in or adjacent to a **hypervariable region** of the parent Ab, where the
inserted amino acid does not bind antigen. The Ab variant comprises a light chain variable domain comprising a CDR L1 sequence consisting of (A1) or (A2). SerAlaThrLysLysIleLysAsnTyrLeuAsn (A1) SerAlaThrLysLysIleThrAsnTyrLeuAsn (A2) Producing an Ab variant comprises culturing the host cell so that the nucleic acid is expressed and recovering the Ab variant from the host cell culture. Determining antigen association rate of an Ab comprises: (a) combining Ab and antigen in solution, and (b) determining formation of Ab-antigen complex over time. Step (2) comprises measuring fluorescence emission intensity of the Ab-antigen complex. The Ab or antigen comprises a tryptophan residue at the antigen-Ab binding interface. The antigen is vascular endothelial growth factor. The Ab has an association constant for antigen slower than 105 M-1 sec-1.

ACTIVITY - Cytostatic. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The method is useful for making an Ab variant of a parent Ab specific to an antigen (claimed) for treating cancer.

ADMINISTRATION - Dosage comprises 1 micrograms to 100 mg per kg body weight. The composition is administered via oral or parenteral routes. (81 pages)

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=> d his

     (FILE 'HOME' ENTERED AT 10:21:13 ON 12 APR 2006)

     FILE 'CAPLUS, BIOENG, BIOTECHNO, BIOTECHDS, ESBIOBASE' ENTERED AT
     10:22:00 ON 12 APR 2006
L1             2 S (HYPERVARIABLE (W) REGION) AND CHIMER? AND (CDR (W) H3)
L2             2 DUPLICATE REMOVE L1 (0 DUPLICATES REMOVED)

=> s (HYPERVARIABLE (W) REGION) AND CHIMER? and insertion and (binding (w) affinity)
L3           2 (HYPERVARIABLE (W) REGION) AND CHIMER? AND INSERTION AND (BINDIN
               G (W) AFFINITY)

=> duplicate remove l3
PROCESSING COMPLETED FOR L3
L4             2 DUPLICATE REMOVE L3 (0 DUPLICATES REMOVED)

=> d l4 bib abs 1=2
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=> s l4 bib abs 1-2
MISSING OPERATOR L4 BIB
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> d l4 bib abs 1-2

L4    ANSWER 1 OF 2  BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
AN    2006-07049  BIOTECHDS
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TI Novel anti-c-met antibody comprising **hypervariable region** (HVR) sequence such as HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2 or HVR-H3, or its variant, useful for treating cancer e.g. lung cancer, brain cancer and kidney cancer;
involving vector-mediated gene transfer and expression in host cell for lung, brain, kidney, gastric, colorectal, pancreas, ovary, head and neck, bladder, mamma and liver cancer, lymphoma, autoimmune disorder and angiogenesis-related disorder diagnosis and therapy

AU DENNIS M S; BILLECI K; YOUNG J; ZHENG Z
PA GENENTECH INC

PI WO 2006015371 9 Feb 2006
AI WO 2005-US27626 4 Aug 2005
PRAI US 2004-598991 5 Aug 2004; US 2004-598991 5 Aug 2004
DT Patent
LA English
OS WPI: 2006-155789 [16]
AN 2006-07049 BIOTECHDS

AB DERWENT ABSTRACT:
NOVELTY - An anti-c-met antibody (I) comprising **hypervariable region** (HVR) sequence chosen from HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2 and HVR-H3, or at least one variant HVR, is new.

DETAILED DESCRIPTION - An anti-c-met antibody (I) is chosen from (a) anti-c-met antibody comprising at least one **hypervariable region** (HVR) sequence chosen from HVR-L1 comprising sequence A1-A17, in which A1-A17 is SEQ ID Number 1, HVR-L2 comprising sequence B1-B7, in which B1-B7 is SEQ ID Number 2, HVR-L3 comprising sequence C1-C9, in which C1-C9 is SEQ ID Number 3, HVR-H1 comprising sequence D1-D10, in which D1-D10 is SEQ ID Number 4, HVR-H2 comprising sequence E1-E18, in which E1-E18 is SEQ ID Number 5, and HVR-H3 comprising sequence F1-F11, in which F1-F11 is SEQ ID Number 6; and at least one variant HVR, where the variant HVR comprises modification of at least one residue of the sequence of SEQ ID Number 1-6, (b) a humanized anti-c-met antibody in which the monovalent affinity of the antibody to human c-met is substantially the same as or at least 3-fold greater than monovalent affinity of a murine antibody comprising a light chain and heavy chain variable sequence of 2 fully defined approximately 114 and 118 amino acid sequences (SEQ ID Number 9 and 10) given in the specification, (c) a humanized anti-c-met antibody capable of inhibiting binding of human hepatocyte growth factor (HGF) to its receptor better than a reference antibody comprising a **chimeric** anti-c-met antibody comprising a light chain and heavy chain variable sequence of SEQ ID Number 9 and 10, (d) a humanized anti-c-met antibody capable of inhibiting human HGF receptor activation better than a reference antibody comprising a **chimeric** anti-c-met antibody comprising a light chain and heavy chain variable sequence of SEQ ID Number 9 and 10, (e) a humanized anti-c-met antibody capable of inhibiting c-met-dependent cell proliferation better than a reference antibody comprising a **chimeric** anti-c-met antibody comprising a light chain and heavy chain variable sequence of SEQ ID Number 9 and 10, (f) an antibody comprising a heavy chain variable domain comprising HVR1-HC, HVR2-HC and/or HVR3-HC sequence of SEQ ID Number 191-193, and (g) an antibody comprising a light chain variable domain comprising HVR1-LC, HVR2-LC and/or HVR3-LC sequence of SEQ ID Number 183-185. The sequences include Lys-Ser-Ser-Gln-Ser-Leu-Leu-Tyr-Thr-Ser-Ser-Gln-Lys-Asn-Tyr-Leu-Ala (SEQ ID Number 1), Trp-Ala-Ser-Thr-Arg-Glu-Ser (SEQ ID Number 2), Gln-Gln-Tyr-Tyr-Ala-Tyr-Pro-Trp-Thr (SEQ ID Number 3), Gly-Tyr-Thr-Phe-Thr-Ser-Tyr-Trp-Leu-His (SEQ ID Number 4), Gly-Met-Ile-Asp-Pro-Ser-Asn-Ser-Asp-Thr-Arg-Phe-Asn-Pro-Asn-Phe-Lys-Asp (SEQ ID Number 5), X-Tyr-Gly-Ser-Tyr-Val-Ser-Pro-Leu-Asp-Tyr (SEQ ID Number 6),
in which X is not R, Lys-Ser-Ser-Gln-Ser-Leu-Leu-Tyr-Thr-Ser-Ser-Gln-Lys-Asn-Tyr-Leu-Ala (SEQ ID Number 183), Trp-Ala-Ser-Thr-Arg-Glu-Ser (SEQ ID Number 184), Gln-Gln-Tyr-Tyr-Ala-Tyr-Pro-Trp-Thr (SEQ ID Number 185), Gly-Tyr-Thr-Phe-Thr-Ser-Tyr-Trp-Leu-His (SEQ ID Number 191),

Gly-Met-Ile-Asp-Pro-Ser-Asn-Ser-Asp-Thr-Arg-Phe-Asn-Pro-Asn-Phe-Lys-Asp (SEQ ID Number 192) and Ala-Thr-Tyr-Arg-Ser-Tyr-Val-Thr-Pro-Leu-Asp-Tyr (SEQ ID Number 193). INDEPENDENT CLAIMS are also included for the following: (1) an antibody (II) comprising a heavy chain variable domain as mentioned in (f) of (I) and a light chain variable domain as mentioned in (g) of (I); (2) a nucleic acid (III) encoding (I) or (II); (3) a host cell comprising (III); and (4) a composition (C1) comprising (I) or (II).

WIDER DISCLOSURE - The following are disclosed: (1) vector comprising (III); and (2) an article of manufacture or a kit comprising (I).

BIOTECHNOLOGY - Preparation: (I) is produced by recombinant DNA technology. Preferred Antibody: In (I), both the humanized antibody and **chimeric** antibody are monovalent, and both the antibodies comprise a single Fab region linked to an Fc region. In (a) of (I), the F1 in a variant HVR-H3 is Thr or Ser, F3 is Arg or Ser and F7 is Thr. (I) is humanized, where at least a portion of the framework sequence is a human consensus framework sequence. The modification is substitution, **insertion** or deletion. The HVR-L2 variant comprises 1-5 (1, 2, 3, 4 or 5) substitutions in any combination of the positions, including B1 (Met or Leu), B2 (Pro, Thr, Gly or Ser), B3 (Asn, Gly, Arg or Thr), B4 (Ile, Asn or Phe), B5 (Pro, Ile, Leu or Gly), B6 (Ala, Asp, Thr or Val) and B7 (Arg, Ile, Met or Gly). The HVR-H1 variant comprises 1-5 (1, 2, 3, 4, or 5) substitutions in any combination of the positions, including D3 (Asn, Pro, Leu, Ser, Ala, Ile), D5 (Ile, Ser or Tyr), D6 (Gly, Asp, Thr, Lys, Arg), D7 (Phe, His, Arg, Ser, Thr or Val) and D9 (Met or Val). The HVR-H2 variant comprises 1-4 (1, 2, 3 or 4) substitutions in any combination of the positions, including E7 (Tyr), E9 (Ile), E10 (Ile), E14 (Thr or Gln), E15 (Asp, Lys, Ser, Thr or Val), E16 (Leu), E17 (Glu, His, Asn or Asp) and E18 (Tyr, Glu or His). The HVR-H3 variant comprises 1-5 (1, 2, 3, 4 or 5) substitutions in any combination of the positions, including F1 (Thr, Ser), F3 (Arg, Ser, His, Thr, Ala, Lys), F4 (Gly), F6 (Arg, Phe, Met, Thr, Glu, Lys, Ala, Leu, Trp), F7 (Leu, Ile, Thr, Arg, Lys, Val), F8 (Ser, Ala), F10 (Tyr, Asn) and F11 (Gln, Ser, His, Phe). (I) comprises HVR-L1 having the sequence of SEQ ID Number 1, and HVR-L3 having the sequence of SEQ ID Number 3, where F1 in a variant HVR-H3 is Thr, F3 in a variant HVR-H3 is Arg or Ser, and F7 in a variant HVR-H3 is Thr. In (b) of (I), the murine antibody is produced by hybridoma cell line deposited under ATCC with designation HB-11894 (hybridoma 1A3.3.13) or HB-11895 (hybridoma 5D5.11.6). The **binding affinity** is expressed as a Kd value, and is measured by Biacore or radioimmunoassay. (I) comprises human kappa subgroup 1 consensus framework sequence, and heavy chain human subgroup III consensus framework sequence. The framework sequence comprises a substitution at position 71, 73 and/or 78. The substitution is R71A, N73T and/or N78A. The (c) of (I) inhibits binding with an IC(50) value that is less than half that of the **chimeric** antibody, where IC(50) is determined across an antibody concentration range from 0.01-1000 nM. The (d) of (I) inhibits receptor activation with IC(50) value that is less than half that of the **chimeric** antibody, where IC(50) is determined across an antibody concentration range from 0.1-100 nM. The (e) of (I) inhibits cell proliferation with IC(50) value that is less than half that of the **chimeric** antibody, where IC(50) is determined across an antibody concentration range from 0.01-100 nM. In (f) of (I), the variable domain comprises FR1-HC, FR2-HC, FR3-HC and/or FR4-HC sequence of SEQ ID Number 187-190, and (I) comprises CH1 and/or Fc sequence of 2 fully defined approximately 108 and 222 amino acid sequences (SEQ ID Number 194 and 195) given in the specification. In (g) of (I), the variable domain comprises FR1-LC, FR2-LC, FR3-LC and/or FR4-LC sequence of SEQ ID Number 179-182, and (I) comprises CL1 sequence of a fully defined approximately 106 amino acid (SEQ ID Number 186) sequence given in the specification. (II) is monovalent, and comprises an Fc region, where the Fc region comprises a first and second polypeptide, where first and second polypeptide each comprises one or more mutations with respect to wild-type human Fc. The first polypeptide comprises the Fc sequence of

SEQ ID Number 195 and second polypeptide comprises a fully defined approximately 223 amino acid (SEQ ID Number 196) sequence given in the specification. Preferred Composition: C1 comprises a carrier. The sequences include Asp-Ile-Gln-Met-Thr-Gln-Ser-Pro-Ser-Ser-Leu-Ser-Ala-Ser-Val-Gly-Asp-Arg-Val-Thr-Ile-Thr-Cys (SEQ ID Number 179), Trp-Tyr-Gln-Gln-Lys-Pro-Gly-Lys-Ala-Pro-Lys-Leu-Leu-Ile-Tyr (SEQ ID Number 180), Gly-Val-Pro-Ser-Arg-Phe-Ser-Gly-Ser-Gly-Ser-Gly-Thr-Asp-Phe-Thr-Leu-Thr-Ile-Ser-Ser-Leu-Gln-Pro-Glu-Asp-Phe-Ala-Thr-Tyr-Tyr-Cys (SEQ ID Number 181), Phe-Gly-Gln-Gly-Thr-Lys-Val-Glu-Ile-Lys-Arg (SEQ ID Number 182), Glu-Val-Gln-Leu-Val-Glu-Ser-Gly-Gly-Gly-Leu-Val-Gln-Pro-Gly-Gly-Ser-Leu-Arg-Ser-Leu-Ser-Cys-Ala-Ala-Ser (SEQ ID Number 187), Trp-Val-Arg-Gln-Ala-Pro-Gly-Lys-Gly-Leu-Glu-Trp-Val (SEQ ID Number 188), Arg-Phe-Thr-Ile-Ser-Ala-Asp-Thr-Ser-Lys-Asn-Thr-Ala-Tyr-Leu-Gln-Met-Asn-Ser-Leu-Arg-Ala-Glu-Asp-Thr-Ala-Val-Tyr-Tyr-Cys (SEQ ID Number 189) and Trp-Gly-Gln-Gly-Thr-Leu-Val-Thr-Val-Ser-Ser (SEQ ID Number 190).

ACTIVITY - Cytostatic; Immunosuppressive; Antiangiogenic. In vivo analysis of the efficacy of anti-c-met antibody in inhibiting tumor was carried out as follows. Athymic female mice were inoculated subcutaneously with KP4 pancreatic carcinoma cells (5 million cells). The mice were injected intraperitoneally with the anti-c-met antibody (OA5D5.v2) or a vehicle (control), twice per week. Tumor size was measured twice per week. The result indicated inhibition of the tumor in the mice treated with the antibody, when compared with the control mice.

MECHANISM OF ACTION - c-met inhibitor; Tyrosine kinase receptor inhbitor; HGF to its receptor; Inhibits HGF receptor activation (all claimed).

USE - (I) or (II) is useful for inhibiting c-met activated cell proliferation, which involves contacting a cell or tissue with (I) or (II); for modulating a disease associated with dysregulation of the HGF/c-met signaling axis, which involves administering (I) or (II) to the subject; and treating a subject having cancer, which involves administering (I) or (II) to the subject, where the cancer is lung cancer, brain cancer, kidney cancer, gastric cancer, colorectal cancer and/or pancreatic cancer. (I) or (II) is useful for treating a proliferative disorder in a subject, which involves administering (I) or (II) to the subject, where the proliferative disorder is cancer (claimed). (I) or (II) is useful for treating immune (autoimmune) disorder and/or an angiogenesis-related disorder. (I) or (II) is useful for diagnosing the diseases as mentioned above. (I) or (II) is useful for treating cancer e.g. ovarian cancer, head and neck cancer, lymphoma, bladder cancer, breast cancer and liver cancer.

ADMINISTRATION - (I) or (II) is administered by parenteral (intramuscular, intravenous, intraarterial, subcutaneous or intraperitoneal), intrapulmonary or intranasal route, at a dosage of 1 micrograms/kg-15 mg/kg, preferably 0.1-10 mg/kg.

EXAMPLE - No relevant example is given.(129 pages)

L4 ANSWER 2 OF 2 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
AN 2003-24971 BIOTECHDS
TI Making an antibody variant of a parent antibody specific to an antigen by identifying a target amino acid residue within the variable domain of the parent antibody and substituting the target residue with a different amino acid residue;
antibody production against antigen via plasmid expression in host cell for use in disease therapy and gene therapy
AU LOWMAN H B; MARVIN J S
PA GENENTECH INC
PI WO 2003068801 21 Aug 2003
AI WO 2003-US4184 11 Feb 2003
PRAI US 2002-409685 10 Sep 2002; US 2002-355895 11 Feb 2002
DT Patent
LA English
OS WPI: 2003-697521 [66]
AN 2003-24971 BIOTECHDS

AB DERWENT ABSTRACT:

NOVELTY - Making an Ab (Ab) variant of a parent Ab specific to an antigen comprising: (a) identifying a target amino acid residue within the variable domain of the parent Ab; and (b) substituting the target residue of step (1) with a different replacement amino acid residue such that the charge complementarity between the Ab and antigen is increased.

DETAILED DESCRIPTION - Making an Ab (Ab) variant of a parent Ab specific to an antigen by (a) identifying a target amino acid residue within the variable domain of the parent Ab, the target residue being an exposed residue in solution, in or adjacent to a **hypervariable region** or within about 20 Angstrom of the antigen when the parent Ab is bound to it; and (b) substituting the target residue of step (1) with a different replacement amino acid residue such that the charge complementarity between the Ab and antigen is increased. INDEPENDENT CLAIMS are also included for: (1) an Ab variant of a parent Ab which comprises an amino acid alteration in or adjacent to a **hypervariable region** of the parent Ab which increases charge complementarity between the Ab variant and an antigen to which it binds; (2) an isolated nucleic acid encoding the Ab variant; (3) a vector comprising the nucleic acid; (4) a host cell transformed with the nucleic acid; (5) a process of producing an Ab variant; and (6) a method for determining antigen association rate of an Ab.

BIOTECHNOLOGY - Preferred Method: Making an Ab variant of a parent Ab specific to an antigen further comprises: (a) producing the Ab variant in a host cell comprising nucleic acid encoding the Ab variant; and (b) conjugating the Ab variant produced by the host cell with a heterologous molecule. The target residue does not directly contact antigen when bound to it. It has at least about one third of its side chain surface area exposed to solvent. It is within at least about 16 Angstrom of the antigen when bound to it. The parent Ab is humanized, human or **chimeric** Ab. It is an Ab fragment, which is a Fab fragment. The Ab variant has a stronger **binding affinity** for the antigen than the parent Ab. The **binding affinity** of the Ab variant is at least about two fold stronger than the **binding affinity** of the parent Ab. The Ab variant has a faster association rate with the antigen than the parent Ab. The association rate of the Ab variant is at least about 5 or 10 fold faster than the association rate of the parent Ab. The Ab variant has 1-20 substitutions in the **hypervariable regions** compared to the parent Ab. Each of the substitutions increases charge complementarity between the Ab and antigen. The antigen is vascular endothelial growth factor (VEGF). The parent Ab comprises the heavy and light chain variable domains of a humanized anti-VEGF Ab consisting of Y0101, Y0317, F(ab)-12, Y0192, Y0238-3, Y0239-19, Y0313-2 or VNERK. The substitution is in a **hypervariable region** consisting of CDR L1, CDR L2, loop H1 or CDR H3. The substitution is at one or more of amino acid positions 26L, 27L, 28L, 30L, 31L, 32L, 50L, 52L, 53L, 54L, 56L, 93L or 94L of a light chain variable domain of the parent Ab, utilizing the residue numbering system according to Kabat. The substitution is at two or more of amino acid positions 26L, 27L, 28L or 30L of a light chain variable domain of the parent Ab, at three or four of amino acid positions 26L, 27L, 28L or 30L of a light chain variable domain of the parent Ab or at one or more of amino acid positions 25H, 28H, 30H, 54H, 56H, 61H, 62H, 99H or 100aH of a heavy chain variable domain of the parent Ab. The antigen is tissue factor (TF). The parent Ab comprises the heavy and light chain variable domains of a humanized anti-TF Ab, which is D3H44. The antigen is HER2. The parent Ab comprises the heavy and light chain variable domains of a humanized anti-HER2 Ab, which is the rhuMAb 4D5. Preferred Ab: The Ab variant of a parent Ab which comprises an amino acid alteration in or adjacent to a **hypervariable region** of the parent Ab. The alteration is an amino acid **insertion** in or adjacent to a **hypervariable region** of the parent Ab, where the inserted amino acid does not bind antigen. The Ab variant comprises a

light chain variable domain comprising a CDR L1 sequence consisting of (A1) or (A2). SerAlaThrLysLysIleLysAsnTyrLeuAsn (A1) SerAlaThrLysLysIleThrAsnTyrLeuAsn (A2) Producing an Ab variant comprises culturing the host cell so that the nucleic acid is expressed and recovering the Ab variant from the host cell culture. Determining antigen association rate of an Ab comprises: (a) combining Ab and antigen in solution, and (b) determining formation of Ab-antigen complex over time. Step (2) comprises measuring fluorescence emission intensity of the Ab-antigen complex. The Ab or antigen comprises a tryptophan residue at the antigen-Ab binding interface. The antigen is vascular endothelial growth factor. The Ab has an association constant for antigen slower than 105 M-1 sec-1.

ACTIVITY - Cytostatic. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The method is useful for making an Ab variant of a parent Ab specific to an antigen (claimed) for treating cancer.

ADMINISTRATION - Dosage comprises 1 micrograms to 100 mg per kg body weight. The composition is administered via oral or parenteral routes.(81 pages)

=> d his

(FILE 'HOME' ENTERED AT 10:21:13 ON 12 APR 2006)

FILE 'CAPLUS, BIOENG, BIOTECHNO, BIOTECHDS, ESBIOBASE' ENTERED AT 10:22:00 ON 12 APR 2006

L1 2 S (HYPERVARIABLE (W) REGION) AND CHIMER? AND (CDR (W) H3)
L2 2 DUPLICATE REMOVE L1 (0 DUPLICATES REMOVED)
L3 2 S (HYPERVARIABLE (W) REGION) AND CHIMER? AND INSERTION AND (BIN
L4 2 DUPLICATE REMOVE L3 (0 DUPLICATES REMOVED)